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Minimum Information about a Biosynthetic Gene cluster

A wide variety of enzymatic pathways that produce specialized metabolites in bacteria, fungi and plants are known to be encoded in biosynthetic gene clusters. Information about these clusters, pathways and metabolites is currently dispersed throughout the literature, making it difficult to exploit. To facilitate consistent and systematic deposition and retrieval of data on biosynthetic gene clusters, we propose the Minimum Information about a Biosynthetic Gene cluster (MIBiG) data standard.

Living organisms produce a range of secondary metabolites with exotic chemical structures and diverse metabolic origins. Many of these secondary metabolites find use as natural products in medicine, agriculture and manufacturing. Research on natural product biosynthesis is undergoing an extensive transformation, driven by technological developments in genomics, bioinformatics, analytical chemistry and synthetic biology. It has now become possible to computationally identify thousands of biosynthetic gene clusters (BGCs) in genome sequences, and to systematically explore and prioritize them for experimental characterization^{1,2}. A BGC can be defined as a physically clustered group of two or more genes in a particular genome that together encode a biosynthetic pathway for the production of a specialized metabolite (including its chemical variants). It is becoming possible to carry out initial experimental characterization of hundreds of such natural products, using high-throughput approaches powered by rapid developments in mass spectrometry^{3–5} and chemical structure elucidation⁶. At the same time, single-cell sequencing and metagenomics are opening up access to new and uncharted branches of the tree of life^{7–9}, enabling scientists to tap into a previously undiscovered wealth of BGCs. Furthermore, synthetic biology allows the redesign of BGCs for effective heterologous expression in preengineered hosts, which will ultimately empower the construction of standardized high-throughput platforms for natural product discovery^{10,11}.

In this changing research environment, there is an increasing need to access all the experimental and contextual data on

characterized BGCs for comparative analysis, for function prediction and for collecting building blocks for the design of novel biosynthetic pathways. For this purpose, it is paramount that this information be available in a standardized and systematic format, accessible in the same intuitive way as, for example, genome annotations or protein structures. Currently, the situation is far from ideal, with information on natural product biosynthetic pathways scattered across hundreds of scientific articles in a wide variety of journals; it requires in-depth reading of papers to confidently discern which of the molecular functions associated with a gene cluster or pathway have been experimentally verified and which have been predicted solely on the basis of biosynthetic logic or bioinformatic algorithms. Although some valuable existing manually curated databases have data models in place to store some of this information^{12–14}, all are specialized towards certain subcategories of BGCs and include just a limited number of parameters defined by the interests of a subset of the scientific community. To enable the future development of databases with universal value, a generally applicable community standard is required that specifies the exact annotation and metadata parameters agreed upon by a wide range of scientists, as well as the possible types of evidence that are associated with each variable in publications and/or patents. Such a standard will be of great value for the consistent storage of data and will thus alleviate the tedious process of manually gathering information on BGCs. Moreover, a comprehensive data standard will allow future data infrastructures to enable the integration of multiple types of data, which will generate new insights that would otherwise not be attainable.

The Genomic Standards Consortium (GSC)¹⁵ (Box 1) previously developed

the Minimum Information about any Sequence (MIxS) framework¹⁶. This extensible ‘minimum information’ standardization framework includes the Minimum Information about a Genome Sequence (MIGS)¹⁷ and the Minimum Information about a MARKer gene Sequence (MIMARKS)¹⁶ standards. MIxS is a flexible framework that can be expanded upon to serve a wide variety of purposes. The GSC facilitates the community effort of maintaining and extending MIxS, and stimulates compliance among the community.

Here, we introduce the “Minimal Information about a Biosynthetic Gene cluster” (MIBiG) specification as a coherent extension of the GSC’s MIxS standards framework. MIBiG provides a comprehensive and standardized specification of BGC annotations and gene cluster-associated metadata that will allow their systematic deposition in databases. Through a community annotation of BGCs that have been experimentally characterized and described in the literature during previous decades, we have constructed an MIBiG-compliant seed dataset. Moreover, a large part of the research community has committed to continue submitting data on newly characterized gene clusters in the MIBiG format in the future. Together, the MIBiG standard and the resulting MIBiG-compliant data sets will allow data infrastructures to be developed that will facilitate key future developments in natural product research.

Design of the MIBiG standard

The MIBiG standard covers general parameters that are applicable to each and every gene cluster as well as compound type-specific parameters that apply only to specific classes of pathways (Fig. 1). Notably, the standard has been designed to be suitable for

A full list of authors and affiliations appears at the end of the paper.

Box 1 | The Genomic Standards Consortium and its MlxS framework

The Genomic Standards Consortium (GSC, <http://gensc.org/>) was founded in 2005 as an open-membership working body with the purpose of promoting the standardization of genome descriptions as well as the exchange and integration of genomic data.

The GSC initiates and coordinates the design of and compliance with several minimum information standards (also known as checklists). An overarching framework has been designed to connect and standardize these checklists themselves: the Minimum Information about any (x) Sequence (MlxS)¹⁶. MlxS consists of three layers.

First, the MlxS standard includes a number of shared descriptors that are relevant to all types of nucleotide sequences, such as collection date, environmental origin, geographical coordinates of the location of origin of the sample and sequencing method.

Second, for a wide range of different environmental origins, so-called 'environmental packages' are available that constitute checklists of

measurements and observations that are specific to each environment: for example, for host-associated microbial DNA samples, the taxonomy of the host, the habitat of the host and several phenotypic characteristics of the host can be collected. In this manner, rich contextual information on the context of each microbial sample is stored.

Third, several checklists are available for specific sequence types, each having their own checklist-specific descriptors. Previous checklists include the Minimum Information about a Genome Sequence (MIGS)¹⁷, Minimum Information about a Metagenome Sequence (MIMS)¹⁷ and Minimum Information about a MARKer gene Sequence (MIMARKS)¹⁶.

In spring 2013, the MIBiG project proposal was accepted by the board of the GSC to form a new checklist within the MlxS framework. Besides a number of general descriptors, it also includes pathway type-specific packages that function analogously, for different classes of biosynthetic pathways, to the way the MlxS environmental packages do for different environmental origins.

biosynthetic pathways from any taxonomic origin, including those from bacteria, archaea, fungi and plants.

The general parameters cover important data items that are universally applicable. First, they include identifiers of the publications associated with the characterization of the gene cluster, so that the full description of the experimental results that support the entire entry can be accessed easily.

The second key group of general parameters describes the associated genomic locus (or loci) and its accession numbers and coordinates, as deposited in or submitted to one of the databases of the International Nucleotide Sequence Database Collaboration (INSDC): the DNA Data Bank of Japan (DDBJ), the European Nucleotide Archive (EBI-ENA) or GenBank, all of which share unified accession numbers. The INSDC accession numbers are also used to link each MIBiG entry (which is given a separate MIBiG accession number) and its annotations to the corresponding nucleotide sequence(s) computationally; hence, a GenBank/ENA/DDBJ submission of the underlying nucleotide sequence is always required to file a MIBiG submission.

The third group of general parameters describes the chemical compounds produced from the encoded pathway, including their structures, molecular masses, biological activities and molecular targets. Additionally, these parameters allow documentation of miscellaneous chemical moieties that are connected to the core scaffold of the molecule (but synthesized independently) and the genes associated with their biosynthesis; this will facilitate the design of tools for the straightforward comparison of such 'sub-clusters', which are frequently present in different variants across multiple parent BGCs.

Finally, there is a group of general parameters describing experimental data on genes and operons in a gene cluster, including gene knockout phenotypes, experimentally verified gene functions and operons verified by techniques such as RNA-seq.

Beside the general parameters, the MIBiG standard contains dedicated class-specific checklists for gene clusters encoding pathways to produce polyketides, nonribosomal peptides (NRPs), ribosomally synthesized and post-translationally modified peptides (RiPPs), terpenes,

saccharides and alkaloids. These include items such as acyltransferase domain substrate specificities and starter units for polyketide BGCs, release/cyclization types and adenylation domain substrate specificities for NRP BGCs, precursor peptides and peptide modifications for RiPP BGCs, and glycosyltransferase specificities for saccharide BGCs. Where applicable, the standard was made compliant with earlier community agreements, such as the recently published classification of RiPPs¹⁸. Hybrid BGCs that cover multiple

**General parameters**

Biosynthetic class(es)*	Functional category of each gene	Chemical database identifier(s)
Key publications*	Tailoring enzymes/reactions*	Compound structure(s)*
Number of loci*	Knockout mutant phenotypes	Compound molecular formula(e)
Complete/partial cluster*	Operon architecture	Exact molecular mass(es)
Nucleotide accession + coordinates*	Functional sub-clusters	Compound activity*
MlxS environmental metadata	Compound name(s)*	Compound molecular target
Custom gene names	Synonyms for compound name(s)	Chemical moieties

Compound type-specific parameters

Polyketides	Nonribosomal peptides	RiPPs
Polyketide subclass*	NRP subclass*	RiPP subclass*
Polyketide synthase type*	Linear/cyclic*	Linear/cyclic*
Linear/cyclic*	NRPS genes*	Precursor-encoding gene(s)*
Starter unit*	Thioesterase type (+ thioesterases)*	Core peptide sequence
Polyketide length**	Release/cyclization type*	Leader peptide length
PKS genes*	Modular NRPS architecture	Follower peptide length
Number of iterations (if iterative)**	Module skipping/iteration**	Cleavage recognition site sequence
Iterative PKS subtype + cyclization type**	Scaffold-modifying NRPS domains	Recognition motif in leader peptide
Trans-acyltransferase genes	Condensation domain subtypes	Peptidases involved in cleavage
Cyclases/aromatases*	A domain substrate specificities	Crosslinks and crosslink types
Thioesterase type (+ thioesterases)**	Epimerization of amino acid	
Release/cyclization type*		Saccharides
Modular PKS architecture**		Saccharide subclass*
Module skipping/iteration**	Terpenoids	Glycosyltransferase (GT) genes
Reductive domains**	Terpene subclass*	GT substrate specificities
Non-reductive modifying PKS domains**	Terpenoid scaffold size*	Sub-clusters for sugar biosynthesis
Ketoreductase stereochemistries	Final isoprenoid precursor*	
AT/CAL domain substrate specificities**	Terpene synthases/cyclases	Alkaloids
	Prenyltransferases	Alkaloid subclass*

Figure 1 | Schematic overview of the MIBiG standard. The MIBiG standard is composed of general and compound class-specific parameters. Wherever relevant, evidence coding is used to indicate the experimental support for items in the checklist. Fields annotated with an asterisk are absolutely mandatory; fields with two asterisks are conditionally mandatory.



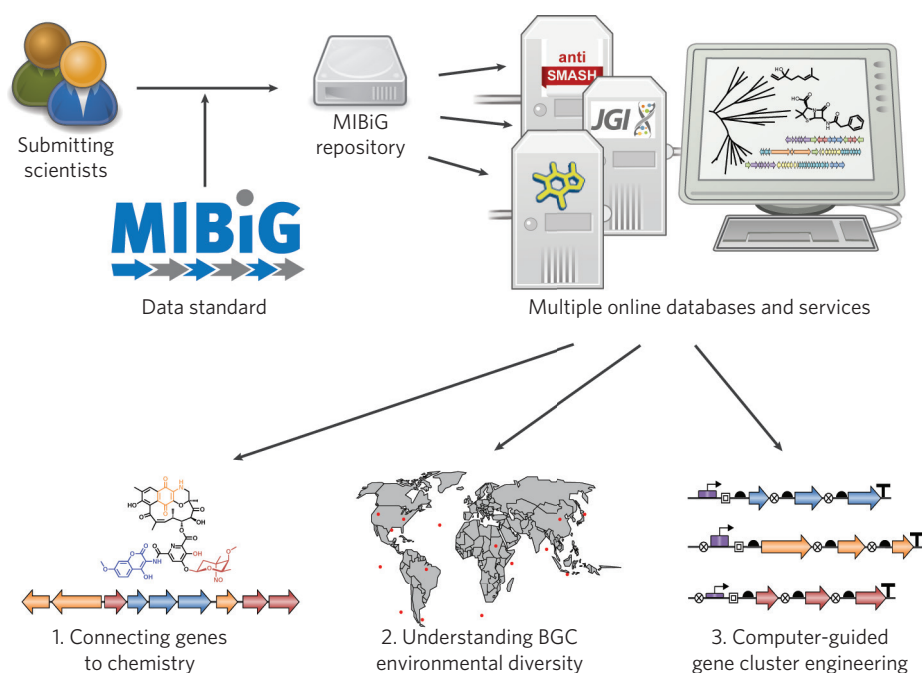


Figure 3 | The MIBiG data standard and submission system will lead to a continuously growing dataset (stored in the online MIBiG repository) that will be loaded into several databases and web services. The lower part of the figure shows the threefold potential of MIBiG for the study of BGCs, which will make it possible to (1) systematically connect genes and chemistry by identifying which genes are responsible for the biosynthesis of which chemical moieties; (2) understand the natural genetic diversity of BGCs within their environmental and ecological context, by combining MIBiG- and MiXS-derived metadata sets; and (3) develop an evidence-based parts registry for engineering biosynthetic pathways and gene clusters through synthetic biology.

analysis of any newly characterized BGCs with a rich source of MIBiG-compliant data. Moreover, this annotation effort offered an ideal opportunity to evaluate the MIBiG standard in practice on a diverse range of BGCs. Hence, we carefully mined the literature to obtain a set of 1,170 experimentally characterized gene clusters: 303 PKS, 189 NRPS, 147 hybrid NRPS-PKS, 169 RiPP, 78 terpene, 123 saccharide, 21 alkaloid and 140 other BGCs. Compared to the 288 BGCs currently deposited in ClusterMine360¹² and the 103 BGCs deposited in DoBISCUIT¹⁴, this presents a significant advance in terms of comprehensiveness. We then annotated each of these 1,170 BGCs with a minimal number of parameters (genomic locus, publications, chemical structure and biosynthetic class and subclass). Subsequently, in a community initiative involving 81 academic research groups and several companies worldwide, we performed a fully MIBiG-compliant reannotation of 405 of these BGCs according to the information available in earlier publications and laboratory archives. (All participants of this annotation effort are either listed as coauthors of this article or mentioned in the Acknowledgments, depending on the size of their contribution.)

An initial visualization of the full data set arising from this reannotation is publicly available online at <http://mibig.secondarymetabolites.org>. Altogether, these submitted entries will function as a very useful seed dataset for the development of databases on secondary metabolism. Future data curation efforts will strive to achieve a fully MIBiG-compliant annotation of the remaining 765 BGCs that are currently annotated with a more restricted set of parameters.

Planned implementation

To allow straightforward and user-friendly access, the MIBiG standard will be implemented by multiple databases and web services for genome data and secondary metabolite research. For example, the MIBiG-curated dataset has already been integrated into the antiSMASH tool in the form of a new module²⁶ that compares any identified BGCs with the full MIBiG-compliant dataset of known BGCs. Moreover, a full-fledged database is currently under development that will be tightly integrated with antiSMASH and will build on the previously published ClusterMine360 framework¹². Additionally, MIBiG-compliant data will be integrated into

the recently released Integrated Microbial Genomes Atlas of Biosynthetic Clusters (IMG-ABC) database from the Joint Genome Institute (<https://img.jgi.doe.gov/ABC/>)²⁷. Regular exchange of data will take place between the MIBiG repository and the IMG-ABC, antiSMASH and ClusterMine databases. Additional cross-links with the chemical databases ChemSpider²⁸, ChEMBL²⁹ and ChEBI³⁰ are being developed so that researchers can easily find the full MIBiG annotation of the BGC responsible for the biosynthesis of given molecules. Finally, all community-curated data are freely available and downloadable in JSON format for integration into other software tools or databases, without any need to request permission, as long as the source is acknowledged.

For submission of new MIBiG-compliant data by scientists in the field, we prepared an interactive online submission form (available from <http://mibig.secondarymetabolites.org>), which was extensively tested through the community annotation effort. Data can also be submitted through the BioSynML plug-in²⁶ (<http://www.biosynml.de>) that was recently built for use in the Geneious software. In this way, MIBiG-compliant data can easily be integrated with the in-house BGC content management systems of individual laboratories or companies. Finally, it will be possible to submit updates to existing MIBiG entries based on peer-reviewed articles through dedicated web forms.

Future perspectives

The MIBiG coordinating team within the GSC is committed to ensuring the continued support and curation of the MIBiG standard, in cooperation with its partners. Compliance with the standard and interoperability with other standards and databases will also be guaranteed within the GSC. In order to stay relevant and viable, MIBiG is projected to be a 'living' standard: updates will be made as needed to remain technologically and scientifically current.

Coordination with relevant journals will be sought to make MIBiG submission of BGCs (evidenced by MIBiG accession codes) a standard item to check during manuscript review. To stimulate submission of MIBiG data during the process of publishing new biosynthetic gene clusters, unique MIBiG accession numbers are provided for each BGC that can be used during article review (including for data embargoed until after publication). The research community represented by this paper commits itself to submitting MIBiG-compliant data sets as well as updates to existing entries when publishing new experimental results on

BGCs. We encourage the larger community to join in this endeavor.

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Author contributions

M.H.M., R.B., E.T. and F.O.G. initiated and coordinated the MIBiG standardization project. M.H.M. designed the first draft of the standard. M.H.M., R.K., P.Y. and F.O.G. coordinated integration within the MixS framework. M.H.M. and R.K. constructed the submission system. M.H.M. and M.C. curated submitted community annotation entries. M.H.M., R.K., P.Y., M.C., R.B., E.T. and F.O.G. wrote the first draft of the paper. All authors contributed to the design of the standard, contributed to the community annotation of MIBiG entries and provided feedback on an early draft of the paper.

Competing financial interests

The authors declare no competing financial interests.

Additional information

Supplementary information is available in the online version of the paper.



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Marnix H Medema^{1,115,*}, Renzo Kottmann¹, Pelin Yilmaz¹, Matthew Cummings², John B Biggins³, Kai Blin⁴, Irene de Bruijn⁵, Yit Heng Chooi^{6–8}, Jan Claesen^{9,10}, R Cameron Coates¹¹, Pablo Cruz-Morales¹², Srikanth Duddela¹³, Stephanie Düsterhus¹⁴, Daniel J Edwards¹⁵, David P Fewer¹⁶, Neha Garg¹⁷, Christoph Geiger¹⁴, Juan Pablo Gomez-Escribano¹⁸, Anja Greule¹⁹, Michalis Hadjithomas¹¹, Anthony S Haines²⁰, Eric J N Helfrich²¹, Matthew L Hillwig²², Keishi Ishida²³, Adam C Jones²⁴, Carla S Jones²⁵, Katrin Jungmann¹³, Carsten Kegler²⁶, Hyun Uk Kim^{4,27}, Peter Kötter¹⁴, Daniel Krug¹³, Joleen Masschelein^{28,29}, Alexey V Melnik¹⁷, Simone M Mantovani³⁰, Emily A Monroe³¹, Marcus Moore³², Nathan Moss³⁰, Hans-Wilhelm Nützmann³³, Guohui Pan³⁴, Amrita Pati¹¹, Daniel Petras³⁵, F Jerry Reen³⁶, Federico Rosconi³⁷, Zhe Rui^{38,39}, Zhenhua Tian⁴⁰, Nicholas J Tobias²⁶, Yuta Tsunematsu^{23,41}, Philipp Wiemann⁴², Elizabeth Wyckoff^{43,44}, Xiaohui Yan³⁴, Grace Yim⁴⁵, Fengan Yu^{46–49}, Yunchang Xie⁵⁰, Bertrand Aigle⁵¹, Alexander K Apel^{52,53}, Carl J Balibar⁵⁴, Emily P Balskus⁵⁵, Francisco Barona-Gómez¹², Andreas Bechthold¹⁹, Helge B Bode^{26,56}, Rainer Borriss⁵⁷, Sean F Brady³, Axel A Brakhage²³, Patrick Caffrey⁵⁸, Yi-Qiang Cheng⁵⁹, Jon Clardy⁶⁰, Russell J Cox^{61,62}, René De Mot⁶³, Stefano Donadio⁶⁴, Mohamed S Donia⁶⁵, Wilfred A van der Donk^{66,67}, Pieter C Dorrestein^{17,30,68}, Sean Doyle⁶⁹, Arnold J M Driessen⁷⁰, Monika Ehling-Schulz⁷¹, Karl-Dieter Entian¹⁴, Michael A Fischbach^{9,10}, Lena Gerwick³⁰, William H Gerwick^{17,30}, Harald Gross^{52,53}, Bertolt Gust^{52,53}, Christian Hertweck^{23,72}, Monica Höfte⁷³, Susan E Jensen⁷⁴, Jianhua Ju⁵⁰, Leonard Katz⁷⁵, Leonard Kaysser^{52,53}, Jonathan L Klassen⁷⁶, Nancy P Keller^{42,77}, Jan Kormanec⁷⁸, Oscar P Kuipers⁷⁹, Tomohisa Kuzuyama⁸⁰, Nikos C Kypides^{11,81}, Hyung-Jin Kwon⁸², Sylvie Lautru⁸³, Rob Lavigne²⁸, Chia Y Lee⁸⁴, Bai Linqun^{85,86}, Xinyu Liu²², Wen Liu⁴⁰, Andriy Luzhetskyy¹³, Taifo Mahmud⁸⁷, Yvonne Mast⁸⁸, Carmen Méndez^{89,90}, Mikko Metsä-Ketelä⁹¹, Jason Micklefield⁹², Douglas A Mitchell⁶⁶, Bradley S Moore^{17,30}, Leonilde M Moreira⁹³, Rolf Müller¹³, Brett A Neilan⁹⁴, Markus Nett²³, Jens Nielsen^{4,95}, Fergal O'Gara^{36,96}, Hideaki Oikawa⁹⁷, Anne Osbourn³³, Marcia S Osburne⁹⁸, Bohdan Ostash⁹⁹, Shelley M Payne^{43,44}, Jean-Luc Pernodet⁸³, Miroslav Petricek¹⁰⁰, Jörn Piel²¹, Olivier Ploux¹⁰¹, Jos M Raaijmakers⁵, José A Salas⁸⁹, Esther K Schmitt¹⁰², Barry Scott¹⁰³,

Ryan F Seipke¹⁰⁴, Ben Shen^{34,105}, David H Sherman^{46–49}, Kaarina Sivonen¹⁶, Michael J Smanski^{106,107}, Margherita Sosio⁶⁴, Evi Stegmann^{53,88}, Roderich D Süssmuth³⁵, Kapil Tahlan³², Christopher M Thomas²⁰, Yi Tang^{6,7}, Andrew W Truman¹⁸, Muriel Viaud¹⁰⁸, Jonathan D Walton¹⁰⁹, Christopher T Walsh¹¹⁰, Tilmann Weber⁴, Gilles P van Wezel¹¹¹, Barrie Wilkinson¹⁸, Joanne M Willey¹¹², Wolfgang Wohlleben^{53,88}, Gerard D Wright⁴⁵, Nadine Ziemert^{53,88}, Changsheng Zhang⁵⁰, Sergey B Zotchev¹¹³, Rainer Breitling², Eriko Takano² & Frank Oliver Glöckner^{1,114}

¹Microbial Genomics and Bioinformatics Research Group, Max Planck Institute for Marine Microbiology, Bremen, Germany. ²Manchester Centre for Synthetic Biology of Fine and Speciality Chemicals (SYNBIOCHEM), Manchester Institute of Biotechnology, Faculty of Life Sciences, University of Manchester, Manchester, UK. ³Laboratory of Genetically Encoded Small Molecules, Howard Hughes Medical Institute, The Rockefeller University, New York, New York, USA. ⁴Novo Nordisk Foundation Center for Biosustainability, Technical University of Denmark, Hørsholm, Denmark. ⁵Netherlands Institute of Ecology (NIOO-KNAW), Department of Microbial Ecology, Wageningen, the Netherlands. ⁶Department of Chemical and Biomolecular Engineering, University of California Los Angeles, Los Angeles, California, USA. ⁷Department of Chemistry and Biochemistry, University of California Los Angeles, Los Angeles, California, USA. ⁸School of Chemistry and Biochemistry, University of Western Australia, Perth, Western Australia, Australia. ⁹Department of Bioengineering and Therapeutic Sciences, University of California San Francisco, San Francisco, California, USA. ¹⁰California Institute for Quantitative Biosciences, University of California San Francisco, San Francisco, California, USA. ¹¹Department of Energy (DOE) Joint Genome Institute, Walnut Creek, California, USA. ¹²Evolution of Metabolic Diversity Laboratory, Unidad de Genómica Avanzada (Langebio), Centro de Investigación y de Estudios Avanzados del Instituto Politécnico Nacional (Cinvestav-IPN), Irapuato, Guanajuato, México. ¹³Helmholtz Institute for Pharmaceutical Research, Helmholtz Centre for Infection Research and Department of Pharmaceutical Biotechnology, Saarland University, Saarbrücken, Germany. ¹⁴Institute for Molecular Biosciences, Goethe University, Frankfurt am Main, Germany. ¹⁵Department of Chemistry and Biochemistry, California State University, Chico, California, USA. ¹⁶Microbiology and Biotechnology Division, Department of Food and Environmental Sciences, University of Helsinki, Helsinki, Finland. ¹⁷Skaggs School of Pharmacy and Pharmaceutical Sciences, University of California San Diego, La Jolla, California, USA. ¹⁸Department of Molecular Microbiology, John Innes Centre, Norwich Research Park, Norwich, UK. ¹⁹Department of Pharmaceutical Biology and Biotechnology, Albert-Ludwigs-University of Freiburg, Freiburg, Germany. ²⁰School of Biosciences, University of Birmingham, Birmingham, UK. ²¹Institute of Microbiology, Eidgenössische Technische Hochschule (ETH) Zürich, Zürich, Switzerland. ²²Department of Chemistry, University of Pittsburgh, Pittsburgh, Pennsylvania, USA. ²³Leibniz Institute for Natural Product Research and Infection Biology (HKI), Jena, Germany. ²⁴Gordon and Betty Moore Foundation, Palo Alto, California, USA. ²⁵Sustainable Studies Program, Roosevelt University Chicago, Illinois, USA. ²⁶Merck Stiftungsprofessur für Molekulare Biotechnologie, Goethe Universität Frankfurt, Fachbereich Biowissenschaften, Frankfurt, Germany. ²⁷Bioinformatics Research Center, Korea Advanced Institute of Science and Technology, Daejeon, Republic of Korea. ²⁸Laboratory of Gene Technology, KU Leuven, Heverlee, Belgium. ²⁹Laboratory of Food Microbiology, KU Leuven, Heverlee, Belgium. ³⁰Center for Marine Biotechnology and Biomedicine, Scripps Institution of Oceanography, University of California San Diego, La Jolla, California, USA. ³¹Department of Biology, William Paterson University, Wayne, New Jersey, USA. ³²Department of Biology, Memorial University of Newfoundland, St. John's, Newfoundland, Canada. ³³Department of Metabolic Biology, John Innes Centre, Norwich Research Park, Norwich, UK. ³⁴Department of Chemistry, The Scripps Research Institute, Jupiter, Florida, USA. ³⁵Institut für Chemie, Technische Universität Berlin, Berlin, Germany. ³⁶BIOMERIT Research Centre, School of Microbiology, University College Cork–National University of Ireland, Cork, Ireland. ³⁷Departamento de Bioquímica y Genómica Microbianas, IBCE, Montevideo, Uruguay. ³⁸Energy Biosciences Institute, University of California Berkeley, Berkeley, California, USA. ³⁹Department of Chemical and Biomolecular Engineering, University of California Berkeley, Berkeley, California, USA. ⁴⁰State Key Laboratory of Bioorganic and Natural Products Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, Shanghai, China. ⁴¹Department of Pharmaceutical Sciences, University of Shizuoka, Shizuoka, Japan. ⁴²Department of Medical Microbiology and Immunology, University of Wisconsin–Madison, Madison, Wisconsin, USA. ⁴³Department of Molecular Biosciences, The University of Texas, Austin, Texas, USA. ⁴⁴Institute for Cellular and Molecular Biology, The University of Texas, Austin, Texas, USA. ⁴⁵Department of Biochemistry and Biomedical Sciences, The M.G. DeGroote Institute for Infectious Disease Research, McMaster University, Hamilton, Ontario, Canada. ⁴⁶Life Sciences Institute, University of Michigan, Ann Arbor, Michigan, USA. ⁴⁷Department of Medicinal Chemistry, University of Michigan, Ann Arbor, Michigan, USA. ⁴⁸Department of Chemistry, University of Michigan, Ann Arbor, Michigan, USA. ⁴⁹Department of Microbiology & Immunology, University of Michigan, Ann Arbor, Michigan, USA. ⁵⁰Key Laboratory of Tropical Marine Bio-resources and Ecology, Guangdong Key Laboratory of Marine Materia Medica, RNAM Center for Marine Microbiology, South China Sea Institute of Oceanology, Chinese Academy of Sciences, Guangzhou, China. ⁵¹Dynamique des Génomes et Adaptation Microbienne, Université de Lorraine and Institut National de la Recherche Agronomique (INRA), Unité Mixte de Recherche (UMR) 1128, Vandœuvre-lès-Nancy, France. ⁵²Pharmaceutical Institute, Department of Pharmaceutical Biology, University of Tübingen, Tübingen, Germany. ⁵³German Centre for Infection Research (DZIF), Partner Site Tübingen, Tübingen, Germany. ⁵⁴Infectious Disease Research, Merck Research Laboratories, Kenilworth, New Jersey, USA. ⁵⁵Department of Chemistry and Chemical Biology, Harvard University, Cambridge, Massachusetts, USA. ⁵⁶Buchmann Institute for Molecular Life Sciences (BMLS), Goethe Universität Frankfurt, Frankfurt, Germany. ⁵⁷Fachbereich Phytomedizin, Albrecht Thaer Institut, Humboldt Universität Berlin, Berlin, Germany. ⁵⁸UCD School of Biomolecular and Biomedical Science, University College Dublin, Dublin, Ireland. ⁵⁹UNT System College of Pharmacy, University of North Texas Health Science Center, Fort Worth, Texas, USA. ⁶⁰Department of Biological Chemistry and Molecular Pharmacology, Harvard Medical School, Boston, Massachusetts, USA. ⁶¹Institut für Organische Chemie, Leibniz Universität Hannover, Hannover, Germany. ⁶²School of Chemistry, University of Bristol, Bristol, UK. ⁶³Centre of Microbial and Plant Genetics, Faculty of Bioscience Engineering, University of Leuven, Heverlee, Belgium. ⁶⁴Naicons Srl, Milano, Italy. ⁶⁵Department of Molecular Biology, Princeton University, Princeton, New Jersey, USA. ⁶⁶Department of Chemistry, University of Illinois at Urbana-Champaign, Urbana-Champaign, Illinois, USA. ⁶⁷Howard Hughes Medical Institute, USA. ⁶⁸Collaborative Mass Spectrometry Innovation Center, University of California San Diego, La Jolla, California, USA. ⁶⁹Department of Biology, Maynooth University, Maynooth, County Kildare, Ireland. ⁷⁰Department of Molecular Microbiology, Groningen Biomolecular Sciences and Biotechnology Institute and Zernike Institute for Advanced Materials, University of Groningen, Groningen, the Netherlands. ⁷¹Functional Microbiology, Institute of Microbiology, Department of Pathobiology, University of Veterinary Medicine Vienna, Vienna, Austria. ⁷²Friedrich Schiller University, Jena, Germany. ⁷³Department of Crop Protection, Faculty of Bioscience Engineering, Ghent University, Ghent, Belgium. ⁷⁴Department of Biological Sciences, University of Alberta, Edmonton, Alberta, Canada. ⁷⁵Synthetic Biology Engineering Research Center (SynBERC), University of California Emeryville, Emeryville, California, USA. ⁷⁶Department of Molecular and Cell Biology, University of Connecticut, Storrs, Connecticut, USA. ⁷⁷Department of Bacteriology, University of Wisconsin–Madison, Madison, Wisconsin, USA. ⁷⁸Institute of Molecular Biology, Slovak Academy of Sciences, Bratislava, Slovak Republic. ⁷⁹Department of Molecular Genetics, Groningen Biomolecular Sciences and Biotechnology Institute, University of Groningen, Groningen, the Netherlands. ⁸⁰Biotechnology Research Center, The University of Tokyo, Tokyo, Japan. ⁸¹Department of Biological Sciences, Faculty of Science, King Abdulaziz University, Jeddah, Saudi Arabia. ⁸²Division of Bioscience and Bioinformatics, Myongji University, Yongin-si, Gyeonggi-Do, South Korea. ⁸³Institute of Integrative Biology of the Cell (I2BC), Commissariat à l'Energie Atomique (CEA), Centre National de la Recherche Scientifique (CNRS), Université Paris Sud, Orsay,

France. ⁸⁴Department of Microbiology and Immunology, University of Arkansas for Medical Sciences, Little Rock, Arkansas, USA. ⁸⁵State Key Laboratory of Microbial Metabolism, Shanghai Jiao Tong University, Shanghai, China. ⁸⁶School of Life Sciences & Biotechnology, Shanghai Jiao Tong University, Shanghai, China. ⁸⁷Department of Pharmaceutical Sciences, Oregon State University, Corvallis, Oregon, USA. ⁸⁸Microbiology/Biotechnology, Interfaculty Institute of Microbiology and Infection Medicine, Faculty of Science, University of Tübingen, Tübingen, Germany. ⁸⁹Departamento de Biología Funcional, Universidad de Oviedo, Oviedo, Spain. ⁹⁰Instituto Universitario de Oncología del Principado de Asturias (I.U.O.P.A.), Universidad de Oviedo, Oviedo, Spain. ⁹¹Department of Biochemistry, University of Turku, Turku, Finland. ⁹²School of Chemistry, University of Manchester, Manchester, UK. ⁹³Institute for Bioengineering and Biosciences, Instituto Superior Técnico, Universidade de Lisboa, Lisboa, Portugal. ⁹⁴School of Biotechnology and Biomolecular Sciences, University of New South Wales, Sydney, New South Wales, Australia. ⁹⁵Department of Chemical and Biological Engineering, Chalmers University of Technology, Gothenburg, Sweden. ⁹⁶Curtin University, School of Biomedical Sciences, Perth, Western Australia, Australia. ⁹⁷Division of Chemistry, Graduate School of Science, Hokkaido University, Sapporo, Japan. ⁹⁸Department of Molecular Biology and Microbiology, Tufts University School of Medicine, Boston, Massachusetts, USA. ⁹⁹Department of Genetics and Biotechnology, Ivan Franko National University of Lviv, Lviv, Ukraine. ¹⁰⁰Institute of Microbiology, Academy of Sciences of the Czech Republic (ASCR), Prague, Czech Republic. ¹⁰¹Laboratoire Interdisciplinaire des Energies de Demain (LIED), UMR 8236 CNRS, Université Paris Diderot, Paris, France. ¹⁰²Novartis Institutes for BioMedical Research, Novartis Campus, Basel, Switzerland. ¹⁰³Institute of Fundamental Sciences, Massey University, Palmerston North, New Zealand. ¹⁰⁴Astbury Centre for Structural Molecular Biology, School of Molecular and Cellular Biology, Faculty of Biological Sciences, University of Leeds, Leeds, UK. ¹⁰⁵Molecular Therapeutics and Natural Products Library Initiative, The Scripps Research Institute, Jupiter, Florida, USA. ¹⁰⁶Department of Biochemistry, Molecular Biology, and Biophysics, University of Minnesota–Twin Cities, Saint Paul, Minnesota, USA. ¹⁰⁷BioTechnology Institute, University of Minnesota–Twin Cities, Saint Paul, Minnesota, USA. ¹⁰⁸Unité BIOlogie et GEstion des Risques en agriculture (BIOGER), Institut National de la Recherche Agronomique (INRA), Grignon, France. ¹⁰⁹Department of Energy Great Lakes Bioenergy Research Center and Department of Energy Plant Research Laboratory, Michigan State University, East Lansing, Michigan, USA. ¹¹⁰Chemistry, Engineering & Medicine for Human Health (ChEM-H) Institute, Stanford University, Stanford, California, USA. ¹¹¹Molecular Biotechnology, Institute of Biology, Leiden University, Leiden, the Netherlands. ¹¹²Hofstra North Shore–Long Island Jewish School of Medicine, Hempstead, New York, USA. ¹¹³Department of Biotechnology, Norwegian University of Science and Technology, Trondheim, Norway. ¹¹⁴Jacobs University Bremen gGmbH, Bremen, Germany. ¹¹⁵Present address: Bioinformatics Group, Wageningen University, Wageningen, the Netherlands.

*e-mail: marnix.medema@wur.nl